PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2000 (15.05.00)	
International application No. PCT/GB99/03284	**Applicant's or agent's file reference** PG3576/PCT
International filing date (day/month/year) 05 October 1999 (05.10.99)	**Priority date** (day/month/year) 05 October 1998 (05.10.98)
Applicant McKEOWN, Stephen, Carl et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 April 2000 (17.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/806892

JC02 Rec'd PCT/PTO 05 APR 2001

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)

Applicant(s): **McKEOWN et al.**

Docket No. **PG3576USW**

Serial No.	Filing Date	Examiner	Group Art Unit
To be assigned	**Concurrently herewith**		

Invention:

CHEMICAL CONSTRUCTS AND THEIR USES

I hereby certify that this **Patent Application under 35 USC 371 and accompanying papers**
(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

April 5 2001
(Date)

Marilyn Eldridge
(Typed or Printed Name of Person Mailing Correspondence)

Marilyn Eldridge
(Signature of Person Mailing Correspondence)

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("Express Mail" Mailing Label No.)

Note: Each paper must have its own certificate of mailing.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

QUILLIN, Helen K
Glaxo Wellcome plc
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 ONN
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 02.01.2001
Applicant's or agent's file reference PG3576/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03284	05/10/1999	05/10/1998

Applicant
GLAXO GROUP LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Michaleczek, N Tel.+49 89 2399-7254

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3576/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03284	05/10/1999	05/10/1998
International Patent Classification (IPC) or national classification and IPC B01J19/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/04/2000	02.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Falls, F Telephone No. +49 89 2399 8350

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03284

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-29	as originally filed	

Claims, No.:

1-25	as originally filed	
26-37	with telefax of	13/12/2000

Drawings, sheets:

1/5-5/5	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

I

1). Prior Art

WO-A-9228640(D1) discloses a combinatorial chemical library comprising a substrate (C-E-C') which may be linked to a solid support by a double linker group F^1 and F^2 (i.e. Su-F^1-F^2-C-E-C'), both of which are cleavable and may be used to sensitize the attached substrate for MS analysis and the use of MS analysis to identify the substrate and follow the reaction history of the substrate. It is considered that this discloses implicitly 2 cleavage sites between the substrate end the support - see Cl's 38 & 39; pg 67, l. 33-36 and Fig's 1-6.

2). Novelty (art. 33(2) PCT)

D1 does not disclose 2 separate linkage groups Y^1 and Y^2 as defined in claim 1 nor a fragment group which comprises the substrate and a portion of the connecting group Y which facilitates instrumental analysis, such as by MS, nor a means for imparting a characteristic signal to the MS of the fragment or to the sensitized molecule for analysis by MS or other instrumental technique. Thus the subject-matter of claims 1 for a chemical construct, claims 28 and 29 for intermediates for forming said construct and claims 32 and 36 for the use of said construct is novel. Independent claims 33 and 34 which refer back directly and indirectly to claim 1 are claims for the use of the chemical construct of claim 1 and their subject-matter is accordingly also novel.

3). Inventive Step (Art. 33(3) PCT)

The application seeks to improve on the existing prior art for monitoring the progress of a chemical reaction to produce a combinatorial library of related compounds.

The use of 2 different linker groups with differential cleavage means that one linker group may be used to sensitize the substrate for MS analysis and the subsequent cleavage of the other means that further molecules of substrate are available for further analysis, thus allowing more than one test to be carried out after a reaction sequence. It also gives other advantages such as the one stated on page 17, l. 11-13 of the description. Such improvement is not suggested in the prior art.

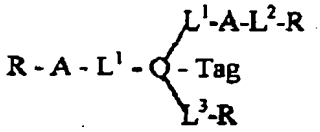
Thus the subject-matter of the claims is inventive.

II

The application does not meet the requirements of the PCT convention in the following respects:

1). The term "drug molecule" has no clear meaning in the art. Therefore claim 3 lacks clarity (Art. 6 PCT).

2). The term Tentagel (pg 21) is a trade mark but has not been designated as such.



wherein L^1, L^2, L^3, A and R are as defined in any one of the preceding claims and "Tag" represents a coding sequence.

26. A construct as claimed in any one of claims 1 to 25 for use in a tiered release method of screening, the construct having the formula Tag - A - L^1 - Q - L^1 - A -L^2 - R wherein Tag, A, L^1, Q ,L^2 and R are as defined in any one of the preceding claims.

27. A chemical construct according to any one of the preceding claims wherein the orthogonally cleavable cleavage sites can be cleaved by a reactions selected from acid catalysed cleavage, base catalysed cleavage, oxidative cleavage, reductive cleavage, nucleophilic displacement, electrophilic displacement, and thermal, photochemical and enzymatic cleavage.

28. Intermediate chemical constructs for use preparing a chemical construct as defined in any one of the preceding claims, the intermediate constructs having the formulae $Y^{1'}$-Q-$Y^{2'}$, RY^1-Q-$Y^{2'}$and $Y^{1'}$-Q-Y^2R wherein $Y^{1'}$ and $Y^{2'}$ are reactive or protected forms of the group Y; and R, Q and Y are as defined in any one of the preceding claims.

29. Intermediate constructs of the formulae $L^{2'}$-A-L^1-Q-L^1-A^P, R-L^2-A-L^1-Q-L^1-A^P, $L^{3'}$-A-L^1-Q-L^1-A^P, R-L^3-A-L^1-Q-L^1-A^P, R-L^3-A-L^1-Q-L^1-A-$L^{2'}$ and $L^{3'}$-A-L^1-Q-L^1-A-L^2-R wherein $L^{1'}$, $L^{2'}$ and $L^{3'}$ are reactive or protected forms of the linker groups L^1, L^2 and L^3, A^P is a reactive or protected form of the spacer group A containing a peak splitting isotopic label, and Q, R, A, L^1, L^2 and L^3 are as defined in any one of the preceding claims.

30. An intermediate construct according to claim 29 wherein the group A^P has the formula NH-Alk-NX^1 wherein Alk is an alkylene group and X^1 is hydrogen or an aralkyl group.

31. An intermediate construct according to claim 29 or claim 30 wherein the solid support has bonded thereto a coding tag sequence L^1-A-Tag and/or a sequence R - A - L^1 -, or a precursor form thereof..

32. A differential release method of assaying a chemical library for biological activity, the method comprising:

(i) subjecting a construct comprising a solid support Q having linked thereto groups Y^1R and Y^2R as defined in any one of the preceding claims to cleavage conditions effective to release substrate R from the group Y^1R;

(ii) testing the substrate R released from the group Y^1R in a biological assay;

(iii) subsequently subjecting the construct to cleavage conditions effective to release substrate R from the group Y^2R; and

(iv)) testing the substrate R released from the group Y^2R in a biological assay.

33. A tiered release method of assaying a chemical library for biological activity, the method comprising:

(i) subjecting a construct as claimed in any one of claims 1 to 27 to cleavage conditions effective to release a first portion of the substrate R from the group Y^1R;

(ii) testing the first portion of substrate R released from the group Y^1R in a biological assay;

(iii) subjecting the construct to cleavage conditions effective to release a second portion of the substrate R from the group Y^1R; and

(iv) testing the second portion of substrate R released from the group Y^1R in a biological assay.

34. A method of determining the identity of a substrate R linked to a solid support Q of a construct as claimed in any one of claims 8 to 27 by mass spectrometric means; the solid support Q having a coding sequence attached thereto by means of a connecting group Y^a having a cleavage site cleavable to release a fragment F^a from the solid support, the fragment F^a comprising the coding sequence and at least a portion of the connecting group Y^a, wherein (i) the chemical fragment F^a contains a sensitising group G which sensitises the chemical fragment F^a to mass spectroscopic analysis;

the coding sequence comprising a sequence of coding groups the nature and order of which is indicative of the identity of the substrate R;

the method comprising cleaving the connecting group Y^a so as to release the fragment F^a from the solid support; subjecting the fragment Y^a to mass spectrometry under conditions effective to bring about mass spectral fragmentation of the coding group and th formation of mass spectral fragment ions corresponding to the loss of one or more coding groups from the coding sequence, and thereafter correlating mass

spectral peaks of the mass spectral fragment ions with the molecular ion of the fragment Y^a to identify the sequence of the individual coding groups.

35. A method according to claim 34 wherein the fragment F^a contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

36. A method of identifying a pharmaceutically useful substrate comprising preparing a library containing a plurality of chemical constructs as defined in any of the preceding claims, and subjecting the library to biological testing to identify biologically active substrates.

37. A method according to claim 36 that includes the further step of formulating a biologically active substrate thus identified with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
Glaxo Wellcome plc
Attn. QUILLIN, Helen K
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
UNITED KINGDOM

Global Intellectual Property
RECEIVED
02 AUG 2000
SH

Date of mailing *(day/month/year)* 28/07/2000	
Applicant's or agent's file reference PG3576/PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 99/03284	International filing date *(day/month/year)* 05/10/1999
Applicant GLAXO GROUP LIMITED et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed Instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer John De Bruijn

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PG3576/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/03284	05/10/1999	05/10/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

ERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B61/00 C07D239/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 37953 A (GLAXO GROUP LTD ;GEYSEN HENDRIK M (US); KINDER DANIEL START (US);) 16 October 1997 (1997-10-16) page 10, line 21 -page 12, line 13 figures 13-17 ---	1,28-37
A	CARRASCO M R ET AL: "Direct Monitoring of Organic Reactions on Polymeric Supports" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 38, no. 36, 8 September 1997 (1997-09-08), pages 6331-6334, XP004087929 ISSN: 0040-4039 page 6331 scheme 1 figure 1 --- -/--	1,28-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/GB 99/03284

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GEYSEN H M ET AL: "ISOTOPE OR MASS ENCODING OF COMBINATORIAL LIBRARIES" CHEMISTRY AND BIOLOGY,GB,CURRENT BIOLOGY, LONDON, vol. 3, no. 8, 1 August 1996 (1996-08-01), pages 679-688, XP002035873 ISSN: 1074-5521 page 679, right-hand column, last paragraph -page 680, left-hand column, paragraph 1 page 686, left-hand column, last paragraph figure 1 ---	1,28-37
A	WO 95 28640 A (UNIV COLUMBIA ;COLD SPRING HARBOR LAB (US); STILL W CLARK (US); WI) 26 October 1995 (1995-10-26) claims 1,38 -----	1,28-37

1

ERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9737953 A	16-10-1997	AU 2723797 A	29-10-1997
		CA 2242171 A	16-10-1997
		CZ 9802176 A	16-12-1998
		EP 0863858 A	16-09-1998
		HU 9901560 A	30-08-1999
WO 9528640 A	26-10-1995	US 5565324 A	15-10-1996
		AU 2292695 A	10-11-1995
		CA 2187792 A	26-10-1995
		CN 1151793 A	11-06-1997
		EP 0755514 A	29-01-1997
		HU 74985 A	28-03-1997
		JP 10502614 T	10-03-1998
		NO 964332 A	03-12-1996
		US 5968736 A	19-10-1999
		US 6001579 A	14-12-1999
		US 5789172 A	04-08-1998

PCT

REQUEST

The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PG3576/PCT

Box No. I TITLE OF INVENTION

Chemical Constructs and their uses

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).*

Glaxo Group Limited
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex
UB6 0NN, GB

☐ This person is also inventor.

Telephone No. 0171 493 4060

Facsimile No. 0181 966 8838

Teleprinter No. 25456

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

McKEOWN, Stephen Carl
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).*

QUILLIN, Helen K.
Glaxo Wellcome plc
Glaxo Wellcome House, Berkeley Avenue
Greenford, Middlesex
UB6 0NN
GB

Telephone No.: 0171-493-4060

Facsimile No.: 0181-966-8838

Teleprinter No.: 25456

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No .2......

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WATSON, Stephen Paul
Glaxo Wellcome plc
Gunnels Wood Road
Stevenage
Hertfordshire
SG1 2NY, GB

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

- ☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

- ☑ **AE** United Arab Emirates
- ☑ **AL** Albania.....
- ☑ **AM** Armenia.....
- ☑ **AT** Austria.....
- ☑ **AU** Australia.....
- ☑ **AZ** Azerbaijan
- ☑ **BA** Bosnia and Herzegovina .....
- ☑ **BB** Barbados
- ☑ **BG** Bulgaria.....
- ☑ **BR** Brazil.....
- ☑ **BY** Belarus.....
- ☑ **CA** Canada
- ☑ **CH and LI** Switzerland and Liechtenstein
- ☑ **CN** China.....
- ☑ **CU** Cuba.....
- ☑ **CZ** Czech Republic.....
- ☑ **DE** Germany.....
- ☑ **DK** Denmark.....
- ☑ **EE** Estonia.....
- ☑ **ES** Spain.....
- ☑ **FI** Finland.....
- ☑ **GB** United Kingdom
- ☑ **GD** Grenada
- ☑ **GE** Georgia.....
- ☑ **GH** Ghana.....
- **GM** Gambia
- ☑ **HR** Croatia .....
- ☑ **HU** Hungary.....
- ☑ **ID** Indonesia
- ☑ **IL** Israel.....
- ☑ **IN** India.....
- ☑ **IS** Iceland
- ☑ **JP** Japan.....
- ☑ **KE** Kenya.....
- ☑ **KG** Kyrgyzstan.....
- ☑ **KP** Democratic People's Republic of Korea.....
- ☑ **KR** Republic of Korea.....
- ☑ **KZ** Kazakstan.....
- ☑ **LC** Saint Lucia
- ☑ **LK** Sri Lanka
- ☑ **LR** Liberia
- ☑ **LS** Lesotho.....
- ☑ **LT** Lithuania
- ☑ **LU** Luxembourg
- ☑ **LV** Latvia
- ☑ **MD** Republic of Moldova.....
- ☑ **MG** Madagascar.....
- ☑ **MK** The former Yugoslav Republic of Macedonia .....
- ☑ **MN** Mongolia
- ☑ **MW** Malawi.....
- ☑ **MX** Mexico.....
- ☑ **NO** Norway
- ☑ **NZ** New Zealand.....
- ☑ **PL** Poland.....
- ☑ **PT** Portugal.....
- ☑ **RO** Romania
- ☑ **RU** Russian Federation.....
- ☑ **SD** Sudan
- ☑ **SE** Sweden
- ☑ **SG** Singapore
- ☑ **SI** Slovenia.....
- ☑ **SK** Slovakia.....
- ☑ **SL** Sierra Leone
- ☑ **TJ** Tajikistan.....
- ☑ **TM** Turkmenistan.....
- ☑ **TR** Turkey.....
- ☑ **TT** Trinidad and Tobago.....
- ☑ **UA** Ukraine.....
- ☑ **UG** Uganda.....
- ☑ **US** United States of America.....
- ☑ **UZ** Uzbekistan.....
- ☑ **VN** Viet Nam.....
- ☑ **YU** Yugoslavia.....
- ☑ **ZA** South Africa
- ☑ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet.

- ☑ **CR** Costa Rica.....
- ☑ **DM** Dominica.....
- ☑ **TZ** Tanzania.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing Date of Earlier Application (day/month/year)	Number Of earlier application	Where earlier application is: national application: country	regional application:* regional Office	International application: receiving Office
item (1) (05.10.98) 05 October 1998	9821669.0	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):_____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earli application was filed (Rue 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional office)*

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	: 4
description (excluding sequence listing part)	: 29
claims	: 8
abstract	: 1
drawings	: 5
sequence listing part of description	:_____
Total number of sheets	**: 47**

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract:

Language of filing of the International application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Helen K. QUILLIN
Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application
2. Drawings ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau

PCT
FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference PG3576/PCT

Applicant

Glaxo Group Limitd et al

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . £55 T

2. SEARCH FEE ..... £638 S

Internation Search to be carried out by_____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application ___47___ sheets.

first 30 sheets . . . . . £285 b_1

17 (remaining sheets) x 6 (additional amount) = £102 b_2

Add amounts entered at b_1 and b_2 and enter total at B . . . . . £387 B

Designation Fees

10 (number of designation fees payable *(maximum 10)*) x 65 (amount of designation fee) = £650 D

Add amounts entered at B and D and enter total at I . £1037 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicant are) so entitled, the total to be entered as I is 25% of the sumof the amounts entered at B and D.

4. FEE FOR PRIORITY DOCUMENT . . . . . P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P,and enter total in the TOTAL box ..... £1730 **TOTAL**

☐ The designation fee is not paid at this time

MODE OF PAYMENT

☒ authorization to charge deposit account (see below)
☐ bank draft
☐ coupons
☐ cheque
☐ cash
☐ other (specify)
☐ postal money order
☐ revenue stamps

Deposit Account Authorization *(this mode of payment may not be available at all receiving Offices)*

The RO/

☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

D01030
Deposit Account Number

5 October 1999
Date *(day/month/year)*

Helen K. Quillin
Signature Helen K. QUILLIN
Agent for the Applicants

15

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3576/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03284	05/10/1999	05/10/1998
International Patent Classification (IPC) or national classification and IPC B01J19/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/04/2000	02.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Falls, F Telephone No. +49 89 2399 8350

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03284

I. Basis f th r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-29	as originally filed	

Claims, No.:

1-25	as originally filed	
26-37	with telefax of	13/12/2000

Drawings, sheets:

1/5-5/5	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

I

1). Prior Art

WO-A-9228640(D1) discloses a combinatorial chemical library comprising a substrate (C-E-C') which may be linked to a solid support by a double linker group F^1 and F^2 (i.e. Su-F^1-F^2-C-E-C'), both of which are cleavable and may be used to sensitize the attached substrate for MS analysis and the use of MS analysis to identify the substrate and follow the reaction history of the substrate. It is considered that this discloses implicitly 2 cleavage sites between the substrate end the support - see Cl's 38 & 39; pg 67, l. 33-36 and Fig's 1-6.

2). Novelty (art. 33(2) PCT)

D1 does not disclose 2 separate linkage groups Y^1 and Y^2 as defined in claim 1 nor a fragment group which comprises the substrate and a portion of the connecting group Y which facilitates instrumental analysis, such as by MS, nor a means for imparting a characteristic signal to the MS of the fragment or to the sensitized molecule for analysis by MS or other instrumental technique. Thus the subject-matter of claims 1 for a chemical construct, claims 28 and 29 for intermediates for forming said construct and claims 32 and 36 for the use of said construct is novel. Independent claims 33 and 34 which refer back directly and indirectly to claim 1 are claims for the use of the chemical construct of claim 1 and their subject-matter is accordingly also novel.

3). Inventive Step (Art. 33(3) PCT)

The application seeks to improve on the existing prior art for monitoring the progress of a chemical reaction to produce a combinatorial library of related compounds.

The use of 2 different linker groups with differential cleavage means that one linker group may be used to sensitize the substrate for MS analysis and the subsequent cleavage of the other means that further molecules of substrate are available for further analysis, thus allowing more than one test to be carried out after a reaction sequence. It also gives other advantages such as the one stated on page 17, l. 11-13 of the description. Such improvement is not suggested in the prior art.

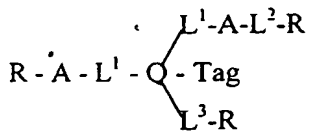
Thus the subject-matter of the claims is inventive.

II

The application does not meet the requirements of the PCT convention in the following respects:

1). The term "drug molecule" has no clear meaning in the art. Therefore claim 3 lacks clarity (Art. 6 PCT).

2). The term Tentagel (pg 21) is a trade mark but has not been designated as such.



wherein L^1, L^2, L^3, A and R are as defined in any one of the preceding claims and "Tag" represents a coding sequence.

26. A construct for use in a tiered release method of screening as described above, the construct having the formula Tag - A - L^1 - Q - L^1 - A -L^2 - R wherein Tag, A, L^1, Q ,L^2 and R are as defined in any one of the preceding claims.

27. A chemical construct according to any one of the preceding claims wherein the orthogonally cleavable cleavage sites can be cleaved by a reactions selected from acid catalysed cleavage, base catalysed cleavage, oxidative cleavage, reductive cleavage, nucleophilic displacement, electrophilic displacement, and thermal, photochemical and enzymatic cleavage.

28. Intermediate chemical constructs for use preparing a chemical construct as defined in any one of the preceding claims, the intermediate constructs having the formulae $Y^{1'}$-Q-$Y^{2'}$, RY^1-Q-$Y^{2'}$and $Y^{1'}$-Q-Y^2R wherein $Y^{1'}$ and $Y^{2'}$ are reactive or protected forms of the group Y; and R, Q and Y are as defined in any one of the preceding claims.

29. Intermediate constructs of the formulae $L^{2'}$-A-L^1-Q-L^1-A^P, R-L^2-A-L^1-Q-L^1-A^P, $L^{3'}$-A-L^1-Q-L^1-A^P, R-L^3-A-L^1-Q-L^1-A^P, R-L^3-A-L^1-Q-L^1-A-$L^{2'}$ and $L^{3'}$-A-L^1-Q-L^1-A-L^2-R wherein $L^{1'}$, $L^{2'}$ and $L^{3'}$ are reactive or protected forms of the linker groups L^1, L^2 and L^3, A^P is a reactive or protected form of the spacer group A containing a peak splitting isotopic label, and Q, R, A, L^1, L^2 and L^3 are as defined in any one of the preceding claims.

30. An intermediate construct according to claim 29 wherein the group A^P has the formula NH-Alk-NX^1 wherein Alk is an alkylene group and X^1 is hydrogen or an aralkyl group.

31. An intermediate construct according to claim 29 or claim 30 wherein the solid support has bonded thereto a coding tag sequence L^1-A-Tag and/or a sequence R - A - L^1 -, or a precursor form thereof..

32. A differential release method of assaying a chemical library for biological activity, the

method comprising:

(i) subjecting a construct comprising a solid support Q having linked thereto groups Y^1R and Y^2R as defined in any one of the preceding claims to cleavage conditions effective to release substrate R from the group Y^1R;

(ii) testing the substrate R released from the group Y^1R in a biological assay;

(iii) subsequently subjecting the construct to cleavage conditions effective to release substrate R from the group Y^2R; and

(iv)) testing the substrate R released from the group Y^2R in a biological assay.

33. A tiered release method of assaying a chemical library for biological activity, the method comprising:

(i) subjecting a construct comprising a solid support Q having linked thereto a group Y^1R as defined in any one of the preceding claims to cleavage conditions effective to release a first portion of the substrate R from the group Y^1R;

(ii) testing the first portion of substrate R released from the group Y^1R in a biological assay;

(iii) subjecting the construct to cleavage conditions effective to release a second portion of the substrate R from the group Y^1R; and

(iv) testing the second portion of substrate R released from the group Y^1R in a biological assay.

34. A method of determining the identity of a substrate R linked to a solid support Q by mass spectrometric means; the solid support Q having a coding sequence attached thereto by means of a connecting group Y^a having a cleavage site cleavable to release a fragment F^a from the solid support, the fragment F^a comprising the coding sequence and at least a portion of the connecting group Y^a, wherein (i) the chemical fragment F^a contains a sensitising group G which sensitises the chemical fragment F^a to mass spectroscopic analysis;

the coding sequence comprising a sequence of coding groups the nature and order of which is indicative of the identity of the substrate R;

the method comprising cleaving the connecting group Y^a so as to release the fragment F^a from the solid support; subjecting the fragment Y^a to mass spectrometry under conditions effective to bring about mass spectral fragmentation of the coding group and the formation of mass spectral fragment ions corresponding to the loss of one or more coding groups from the coding sequence, and thereafter correlating mass

spectral peaks of the mass spectral fragment ions with the molecular ion of the fragment Y^a to identify the sequence of the individual coding groups.

35. A method according to claim 34 wherein the fragment F^a contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

36. A method of A method of identifying a pharmaceutically useful substrate comprising preparing a library containing a plurality of chemical constructs as defined in any of the preceding claims, and subjecting the library to biological testing to identify biologically active substrates.

37. A method according to claim 36 that includes the further step of formulating a biologically active substrate thus identified with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

[redacted]ENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PG3576/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 03284	05/10/1999	05/10/1998
Applicant		
GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

Inter[redacted]nal Application No
PC[redacted]B 99/03284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B61/00 C07D239/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A ✓	WO 97 37953 A (GLAXO GROUP LTD ;GEYSEN HENDRIK M (US); KINDER DANIEL START (US);) 16 October 1997 (1997-10-16) page 10, line 21 -page 12, line 13 figures 13-17 ---	1,28-37
A ✓	CARRASCO M R ET AL: "Direct Monitoring of Organic Reactions on Polymeric Supports" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 38, no. 36, 8 September 1997 (1997-09-08), pages 6331-6334, XP004087929 ISSN: 0040-4039 page 6331 scheme 1 figure 1 --- -/--	1,28-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

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INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 99/03284

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A ✓	GEYSEN H M ET AL: "ISOTOPE OR MASS ENCODING OF COMBINATORIAL LIBRARIES" CHEMISTRY AND BIOLOGY,GB,CURRENT BIOLOGY, LONDON, vol. 3, no. 8, 1 August 1996 (1996-08-01), pages 679-688, XP002035873 ISSN: 1074-5521 page 679, right-hand column, last paragraph -page 680, left-hand column, paragraph 1 page 686, left-hand column, last paragraph figure 1 ---	1,28-37
A ✓	WO 95 28640 A (UNIV COLUMBIA ;COLD SPRING HARBOR LAB (US); STILL W CLARK (US); WI) 26 October 1995 (1995-10-26) claims 1,38 -----	1,28-37

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/ 99/03284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9737953 A	16-10-1997	AU 2723797 A	29-10-1997
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		EP 0863858 A	16-09-1998
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(11) International Publication Number: WO 00/20112

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(21) International Application Number: PCT/GB99/03284

(22) International Filing Date: 5 October 1999 (05.10.99)

(30) Priority Data:
9821669.0 5 October 1998 (05.10.98) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: McKEOWN, Stephen, Carl [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WATSON, Stephen, Paul [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: QUILLIN, Helen, K.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: CHEMICAL CONSTRUCTS AND THEIR USES

(57) Abstract

The invention provides a chemical construct for use in solid phase synthesis comprising a solid support Q having linked thereto groups Y^1R and Y^2R; wherein R is a substrate or a coding tag and the groups Y^1 and Y^2 are connecting groups each having a first cleavage site, at least one of Y^1 and Y^2 having a second cleavage site located between the first cleavage site and group R, the first cleavage site being orthogonally and selectively cleavable with respect to the second cleavage site, and, when both groups Y^1 and Y^2 contain a second cleavage site, the second cleavage site in Y^1 being selectively and orthogonally cleavable with respect to the second cleavage site in Y^2; the second cleavage site being cleavable to release the substrate; and the first cleavage site being selectively cleavable to release a fragment Fr comprising the substrate R and at least a portion of the connecting group Y; and wherein: (i) the chemical fragment Fr contains a sensitising group G which sensitises the chemical fragment Fr to instrumental, e.g. mass spectroscopic analysis; and/or (ii) the fragment Fr contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

(11) International Publication Number: WO 00/20112

(43) International Publication Date: 13 April 2000 (13.04.00)

(21) International Application Number: PCT/GB99/03284

(22) International Filing Date: 5 October 1999 (05.10.99)

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26 October 2000 (26.10.00)

(54) Title: CHEMICAL CONSTRUCTS AND THEIR USES

(57) Abstract

The invention provides a chemical construct for use in solid phase synthesis comprising a solid support Q having linked thereto groups Y^1R and Y^2R; wherein R is a substrate or a coding tag and the groups Y^1 and Y^2 are connecting groups each having a first cleavage site, at least one of Y^1 and Y^2 having a second cleavage site located between the first cleavage site and group R, the first cleavage site being orthogonally and selectively cleavable with respect to the second cleavage site, and, when both groups Y^1 and Y^2 contain a second cleavage site, the second cleavage site in Y^1 being selectively and orthogonally cleavable with respect to the second cleavage site in Y^2; the second cleavage site being cleavable to release the substrate; and the first cleavage site being selectively cleavable to release a fragment Fr comprising the substrate R and at least a portion of the connecting group Y; and wherein: (i) the chemical fragment Fr contains a sensitising group G which sensitises the chemical fragment Fr to instrumental, e.g. mass spectroscopic analysis; and/or (ii) the fragment Fr contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 99/03284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B61/00 C07D239/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 37953 A (GLAXO GROUP LTD ;GEYSEN HENDRIK M (US); KINDER DANIEL START (US);) 16 October 1997 (1997-10-16) page 10, line 21 -page 12, line 13 figures 13-17 ---	1,28-37
A	CARRASCO M R ET AL: "Direct Monitoring of Organic Reactions on Polymeric Supports" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 38, no. 36, 8 September 1997 (1997-09-08), pages 6331-6334, XP004087929 ISSN: 0040-4039 page 6331 scheme 1 figure 1 --- -/--	1,28-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 99/03284

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 95 28640 A (UNIV COLUMBIA ;COLD SPRING HARBOR LAB (US); STILL W CLARK (US); WI) 26 October 1995 (1995-10-26) claims 1,38 -----	1,28-37

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 99/03284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9737953 A	16-10-1997	AU 2723797 A	29-10-1997
		CA 2242171 A	16-10-1997
		CZ 9802176 A	16-12-1998
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